Immunologic Assessment in Patients with Prostatic Carcinoma

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The role of immune mechanisms in the development and control of prostatic carcinoma appears to be complicated by the endocrine response of some tumors. The progression of endocrine-independent tumors is more directly related to host-immune response. Evaluation of the role of chemotherapeutic agents must include their effect on the host-immune response. The use of BCG in patients with metastatic prostatic carcinoma produces no alteration in cell-mediated immunity but produces local tumor necrosis. The use of nonspecific antigens to enhance host-immune response may be more effective when used as adjuvant therapy in earlier stages of prostatic adenocarcinoma.

Immunologic evaluation of patients with urologic carcinoma has been used to obtain a correlation between immune responsiveness and tumor progression.1-3 This information could lead to improved management of these patients by avoiding or limiting therapy which might depress immune response.4 Alternately or additionally, a nonspecific or tumor-specific antigen might enhance the immune response to limit tumor extension.2,5

The presence or absence of cell-mediated immunocompetence correlates very closely to the disease stage in bladder carcinoma.3,6 Preliminary studies of immunocompetence in patients with carcinoma of the prostate are conflicting.7 Catalona and associates found no correlation between lack of immunocompetence and tumor stage with carcinoma of the prostate.8 Huus and Perskey, alternatively, found a direct correlation between DNBC reactivity and tumor stage.7 They suggested that a careful evaluation of tumor stage is important to the proper assessment of reactivity with carcinoma of the prostate. However, when the patients receiving endocrine therapy are eliminated from Catalona’s series, tumor progression correlates very closely with immune response. It must be noted that the exact role of host-immune response with carcinoma of the prostate may be altered when hormone dependent tumors are present.
The cell-mediated response in carcinoma of the prostate is altered by what appears to be two different mechanisms. Serum factors have been shown to produce an impaired lymphocytic reactivity to phytohemagglutinin (PHA). This may be the result of a blocking antibody, probably present in the A2 globulin fraction. A second mechanism appears to involve a decrease in the absolute lymphocyte count as well as ability of these lymphocytes to react to PHA when incubated with normal serum.

Alteration of immune response may play a significant role in the progression of prostatic carcinoma. Present modes of therapy have shown they may alter lymphocyte response and total lymphocytic counts. The ultimate role of these responses is not yet fully apparent but is the subject of further investigation.

**Radiation therapy**

Patients in all stages of prostatic carcinoma, who had a course of radiation therapy within 12 months of lymphocyte counts, showed significant depression of total and T lymphocyte counts. This reduction was greater in patients with metastatic disease. It would appear that recovery of lymphocyte counts requires a minimum of 24 months. During this period of immune suppression, metastatic disease may escape immune controls. It would seem logical during this time to attempt to enhance immune response or to use adjuvant chemotherapy or endocrine therapy.

**Chemotherapy**

Agents with antiproliferative properties against lymphocytes are being used more and it is well to recognize their effect in the total management of prostatic carcinoma.

Cyclophosphamide produces a profound leukopenia within 7 to 12 days. It also has the potential to induce specific tolerance when administered during the inductive phase of immune response. Mounting evidence suggests that cyclophosphamide has a preferential effect on B lymphocytes. Thus, the reduction of enhancing antibodies by B lymphocyte suppression may increase cellular tumor cytotoxic activity.4

**5-Fluoruracil**

This agent exerts its antineoplastic effect during the S phase of the cell cycle. In therapeutic doses it suppresses delayed hypersensitivity and antibody production. It would appear that immunosuppression with this drug might allow tumor escape and progression. The depression of lymphocyte levels with this agent is reflected in a moderate T lymphocyte reduction. The most interesting observation is with 5-FU-induced tumor remission where T lymphocyte counts rebounded to above pretreatment levels. This may be explained by a reduction of tumor bulk and, therefore, serum factors which may suppress lymphocyte proliferation. To evaluate properly the antineoplastic agent's capabilities to control tumor growth, it is apparent that concurrent host immune monitoring is essential.

**Estrogen therapy**

(Diethyl Stilbesterol 1 mg/d Chlorotrianisene 12 mg/d)

In patients treated with these estrogens phytohemagglutinin-stimulated blastogenesis was depressed. Despite this finding, there was an elevation in the absolute lymphocyte and monocyte counts as well as improved delayed cutaneous hypersensitivity response to PPD. Examination of humoral immune parameters showed an increase in the total protein most evident in the Alpha 2 globulin.

Caution must be exerted in interpreting the host-immune response during estrogen therapy, particularly if significant tumor volume reduction occurs during this time. It would seem that, if the total immune response is depressed during estrogen therapy, an approach to combined therapy with im-
mune stimulation or pulse endocrine therapy should be considered.

Orchiectomy

Studies, in a small group of patients, of lymphocyte populations pre- and post-orchiectomy produced inconclusive evidence. Improved absolute lymphocyte counts were reported in 3 of 5 patients. However, indications of tumor volume alterations were not noted. It would seem that considerable study should be directed to investigation of host-immune response pre-and post-orchiectomy.

BCG-Bacillus Calmette Guerin

This antigen has been used to produce some dramatic responses with melanomas. Its use with prostatic carcinoma has been limited. The modes of administration have been oral as well as intralesional. Oral BCG failed to produce any improvement in cellular immune response or tumor regression.

Intralional injection produces localized tumor necrosis but fails to induce any change in cellular immune response. Side effects of intralional injections occurred with the third and fourth injections and consisted of fever. Anaphylactic reaction has been reported with intralional injection. The poor response to BCG in patients with advanced prostatic cancer may indicate a need for other modes of therapy to reduce tumor bulk prior to immunotherapy. The need for evaluation of other antigens (corynibacterium parvum, KLH) and other sites of introduction (bladder, lower extremity) appears indicated in future attempts to enhance the immune response.

References


